Renal denervation: potential impact on hypertension in kidney disease?

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About a year ago, the introduction of catheter-based renal denervation was briefly mentioned in an editorial in *Nephrology Dialysis Transplantation* [1]. In view of recent new data, it is appropriate to discuss this novel method and its implications in kidney disease in greater detail. In the following, we shall briefly discuss the underlying rationale, the potential clinical relevance and some unresolved issues.

**Sympathetic activity and the kidney**

Various hypertensive conditions are characterized by sympathetic hyperactivity, including (some forms of) essential hypertension, metabolic syndrome/obesity, sleep apnea and—of particular relevance to the nephrologist—chronic kidney disease (CKD). Even in the absence of hypertension, heart failure is often associated with sympathetic hyperactivity. Research over the past two decades has convincingly shown that the kidneys are important in the pathogenesis of sympathetic hyperactivity.

Kidney ischaemia is the central mechanism stimulating the renin–angiotensin system (RAS) and of high sympathetic nerve activity [2]. Even a minute lesion by injection of phenol into one kidney caused increased central sympathetic activity and hypertension [3]. Conversely, renal denervation or unilateral nephrectomy reduces or totally prevents hypertension [4]. Long-term low-dose angiotensin II infusion in rats produces a gradual increase in blood pressure; kidney denervation partially prevented hypertension, illustrating the role of sympathetic overactivity in this model [5]. The kidney transplantation model provided convincing evidence that angiotensin II receptors in the kidney are of crucial importance in the pathogenesis of angiotensin II-mediated hypertension and organ damage [6]. What is the role of sympathetic activity in this context? Angiotensin II acts on different levels i.e. the kidney, the central nervous system (CNS) and peripheral sites to provoke noradrenaline release from sympathetic nerve terminals. Whether the effects of kidney injury on sympathetic nerve activity at the kidney level are direct or mediated via angiotensin II is unclear. Increased sympathetic activity enhances the activity of the RAS, suggesting reciprocal potentiation of the two systems. So, kidney injury which is generally characterized by increased RAS activity can increase sympathetic nerve activity and cause hypertension as well as organ damage. Because all these abnormalities are largely prevented by destruction of the renal nerves, renal innervation must obviously play a crucial role.

Can one extrapolate from these animal data to humans? Yes, there is convincing evidence that these mechanisms are also operational in humans. Converse *et al.* [7] were the first to show that muscle sympathetic nerve activity (MSNA) is increased in CKD patients; this method captures sympathetic activity originating in the CNS acting downstream on resistance vessels. Importantly, in bilaterally nephrectomized patients MSNA was comparable to controls [7, 8]. These and other findings provide definite proof that diseased kidneys trigger sympathetic overactivity. Variables of the circulating RAS are undetectable after bilateral nephrectomy [9]. The interaction between the RAS and the sympathetic system is illustrated by the observation that there is parallel activation of the renin and the sympathetic systems in CKD patients [2]. Furthermore both in normal controls and in CKD patients, the activity of both systems shifts in parallel with changes in fluid status [10]. The hypothesis of a cause and effect relation (or a common origin) is supported by the observation that intravenous infusion of angiotensin II stimulates MSNA in humans [11].

Taking together all available data, it seems logical to conclude that there are (at least) two types of sympathetic activity of central origin acting on resistance vessels:

- on the one hand ‘baseline’ activity under control of the CNS and the baroreceptor which is seen both in healthy persons and even in bilaterally nephrectomized patients;
- on the other hand sympathetic ‘overactivity’ as a result of stimuli originating in the diseased kidneys. The latter closely correlates with the activation of the RAS. What triggers the renal signal? Presumably ischaemia. Even small lesions which do not affect kidney function can lead to this chain of events [3, 4]. It is therefore likely...
that this sequence, as schematically shown in the Figure 1, is operational in many disease conditions.

Does sympathetic activity affect outcomes other than blood pressure? There is abundant evidence clearly linking sympathetic hyperactivity with poor clinical outcomes including left ventricular mass, vascular hypertrophy, kidney failure progression and risk of cardiovascular mortality risk as discussed in more detail elsewhere [2, 12, 13].

Renal denervation

Given the above information, it is not surprising that renal denervation might be a useful treatment strategy. Indeed, half a century ago, before the availability of antihypertensive agents, severely hypertensive patients were subjected to surgical denervation of the kidneys [14, 15]. This invasive procedure was abandoned because of severe side effects and the introduction of antihypertensive agents.

Recently, the concept of renal denervation experienced a renaissance by the far less side effect-prone method of catheter-based renal denervation. Both afferent and efferent renal nerves are located in the wall of the renal artery. The technique of catheter-based renal denervation resembles an ordinary arteriogram. Energy is generated by a radiofrequency generator and applied on various spots of the wall of renal arteries thus irreversibly destroying the nerves. First results of a feasibility study were obtained in a group of ~50 patients with uncontrolled hypertension despite three antihypertensive agents. In this observational study, blood pressure decreased considerably in the course of the subsequent 12 months [16]. More recently, observational data were presented suggesting that the effect was still present after >24 months (presentation at the 2010 European Society of Cardiology meeting in Stockholm). In one patient, MSNA, assessed in the peroneal nerve, was reduced after the

![Central nervous system](https://academic.oup.com/ndt/article-abstract/26/9/2732/1819627/28/19627/9?324)

Fig. 1. Schematic representation of the kidney involvement in the pathogenesis of sympathetic hyperactivity. Minimal kidney damage, not necessarily affecting kidney function, results in area(s) of ischemia. Increased plasma levels of angiotensin II and/or increased afferent renal nerve activity stimulates the central nervous system to increase central sympathetic outflow.

For several reasons, these data are potentially of relevance, including of relevance to the nephrologist. First, they suggest that a single intervention has an antihypertensive effect lasting for prolonged periods of time, maybe even years. Presently, it has only been tested in so-called resistant hypertension, defined as systolic blood pressure >160 mmHg despite three or more antihypertensive agents. Second, given the convincing evidence linking sympathetic hyperactivity to poor clinical outcomes, it will be relevant to quantify the effects on clinical outcomes beyond blood pressure. Third, when data on longer term safety and efficacy of the procedure are available, it will be of interest whether other conditions may also benefit from this intervention, e.g. less severe hypertension, metabolic syndrome/obesity, sleep apnea, CKD and heart failure. If a prolonged effect is demonstrated, it is likely that the procedure can be (very) cost-effective.

There is another reason why the introduction of this procedure is important. It will teach us more about the pathophysiology. The fact that this very localized single intervention has such pronounced systemic effects can only be explained by the pathophysiologic model outlined above and schematically shown in the Figure 1. It will be particularly interesting to study in which patients this intervention is effective and in which it is not and also to work out predictors for the efficacy of the procedure. Given the fact that in experimental models, hypertension is prevented by denervation, one might raise the question why in humans it is only partially reduced. In this context, it is intriguing that available observational data suggest that the effects on blood pressure are increasing over time. It seems attractive to hypothesize that apart from a direct effect of the intervention on blood pressure, there may be a second level of efficacy, i.e. the slow reversal of structural vascular and/or renal abnormalities. It seems logical that this takes some time to occur. Another explanation for a partial, instead of (near) total, reduction in blood pressure toward normal levels could be that the procedure is only partially effective in destroying the nerves. Variability in efficacy of the denervation procedure itself may also explain the variability of the magnitude of the antihypertensive effect between subjects. From a theoretical point of view, MSNA assessment is the ideal method to evaluate the efficacy of the procedure. Unfortunately, this is unsuitable in every day clinical practice. Further, there are also nerves around the veins and ureters. The precise contribution of these nerves to circulatory functions is unclear. A suitable human ‘model’ to test the effects of total renal denervation, is unavailable, except for total nephrectomy. Experimental evidence shows that nephrectomy of an injured kidney results in (almost) complete normalization of blood pressure [3]. Finally, incomplete normalization of elevated blood pressure may be explained by the assumption that
other blood pressure-increasing mechanisms may remain operational. It is important to realize that remaining circulating angiotensin II exerts a direct effect on the vasculature as well as on the sympathetic system, the latter both on the level of CNS and the periphery.

Another interesting challenge is the fact that this ‘clean’ method of sympatholytic therapy makes it possible to study the influence of sympathetic activity on various pathologies. For instance, it has been hypothesized that the interaction between insulin resistance and sympathetic activity might be bidirectional. First results seem to suggest that insulin sensitivity improves considerably after renal denervation, strongly supporting the role of sympathetic hyperactivity in its pathogenesis. Other interesting subjects could be the effect on inflammatory markers and on markers of vascular, renal haemodynamic and cardiac function and structure.

Are there any downsides? Obviously, there is concern about a detrimental effect on the anatomy of the renal arteries with this invasive procedure. Careful long-term follow-up of these patients is therefore mandatory. Regeneration of nerve function is very well possible, especially for efferent nerves. Afferent nerves are unlikely to regrow. Any anatomical and functional regeneration will be difficult to diagnose apart from a rise in blood pressure. However, given the above-mentioned pathophysiologic considerations, effects on afferent nerves are likely to be (much) more important than any effect on efferent nerves. It seems unlikely, that there are unwanted effects with respect to short-term blood pressure regulation, since baroreceptor function is not affected. Because both afferent and efferent nerves may be destroyed, water and salt regulation by the kidney may be altered. No data on that subject are available so far. Finally, the procedure is still expensive.

Conclusion
Catheter-based renal denervation offers a fascinating novel treatment modality. The recently presented data provide sufficient rationale for further research on this methodology. The way to do this is by careful and detailed long-term analysis of efficacy and safety variables in patients before and after the procedure. The procedure may also promote a better understanding of the underlying pathophysiology, thus helping to define which type of patients will especially benefit from the procedure. Future research should also include cost-effectiveness analysis.

References

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